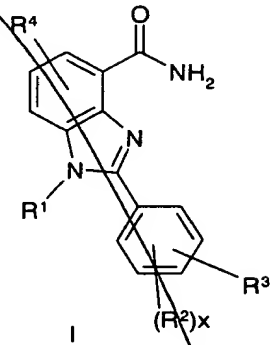
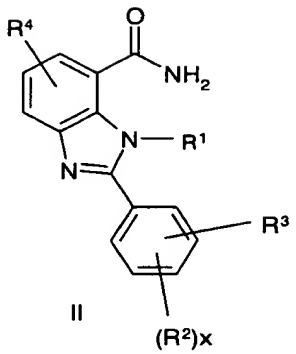
We claim:

1. A compound of the formula I or II



I



II

in which

R^1 is hydrogen, branched and unbranched C_1-C_6-alkyl, it also being possible for one C atom of the alkyl radical to carry OR^{11} or a group R^5, where
R^{11} is hydrogen or C_1-C_4-alkyl, and

R^2 is hydrogen, chlorine, bromine, iodine, fluorine, CF_3, nitro, $NHCOR^{21}$, $NR^{22}R^{23}OH$, O-C_1-C_4-alkyl, O-C_1-C_4-alkylphenyl, NH_2, phenyl, it also being possible for the phenyl rings to be substituted by at most two radicals R^{24}, and R^{21} and R^{22} independently of one another are hydrogen or C_1-C_4-alkyl and R^{23} is hydrogen, C_1-C_4-alkyl or phenyl, and R^{24} is OH, C_1-C_6-alkyl, O-C_1-C_4-alkyl, chlorine, bromine, iodine, fluorine, CF_3, nitro, NH_2, and

x may be 0, 1 or 2 and

R^3 is $-D-(F^1)_p-(E)_q-(F^2)_r-G$, where p, q and r may not simultaneously be 0, or is $-E-(D)_u-(F^2)_s-(G)_v$, it also being possible for the radical E to be substituted by one or two radicals A, or R^3 is B and

R^4 is hydrogen, chlorine, fluorine, bromine, iodine, branched and unbranched C_1-C_6-alkyl, OH, nitro, CF_3, CN, $NR^{41}R^{42}$, NH-CO-R^{43}, O-C_1-C_4-alkyl, where
R^{41} and R^{42} independently of one another are hydrogen or C_1-C_4-alkyl and

R^{43} is hydrogen, C_1-C_4-alkyl, C_1-C_4-alkylphenyl or phenyl, and

D is S or O,

E is phenyl, imidazole, pyrrole, thiophene, pyridine, pyrimidine, piperazine, pyrazine, furan, thiazole, isoxazole, pyrrolidine, piperidine, trihydroazepine and

F^1 is a chain of 1 to 8 carbon atoms, it also being possible for one carbon atom of the chain to carry an OH or O-C_1-C_4-alkyl group and

F^2 is a chain of 1 to 8 carbon atoms, it also being possible for one carbon atom of the chain to carry an OH or O-C_1-C_4-alkyl group and

p may be 0 or 1 and

q may be 0 or 1, and

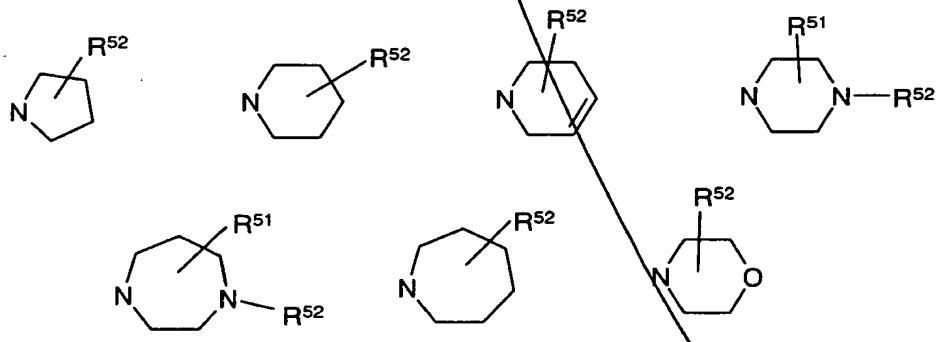
r may be 0 or 1 and

s may be 0 or 1 and

u may be 0 or 1 and

v may be 0 or 1

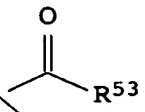
G may be $NR^{51}R^{52}$ or



and

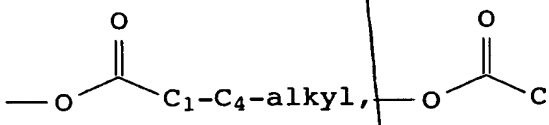
R^{51} is hydrogen or branched and unbranched C_1-C_6-alkyl, $(CH_2)_t$-K and

R^{52} is hydrogen, branched and unbranched C_1-C_6-alkyl, phenyl,


, $-SO_2R^{53}$, $-(C=N)-R^{53}$, $-CO-NHR^{53}$, $-(C=N)-NHR^{53}$,

in which

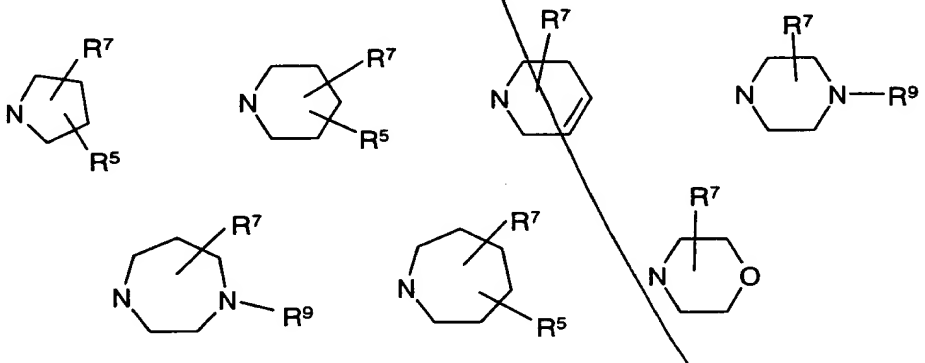
R^{53} may be branched or unbranched $O-C_1-C_6$-alkyl, phenyl, branched or unbranched C_1-C_4-alkylphenyl, where in the case of R^{52} and R^{53} independently of one another one hydrogen of the C_1-C_6-alkyl radical may be substituted by one of the following radicals: OH, $O-C_1-C_4$-alkyl, cyclohexyl, cyclopentyl, tetrahydronaphthyl, cyclopropyl, cyclobutyl, cycloheptyl, naphthyl and phenyl, it also being possible for the carbocycles of the radicals R^{52} and R^{53} independently of one another to carry one or two of the following radicals: branched or unbranched C_1-C_6-alkyl, branched or unbranched $O-C_1-C_4$-alkyl, OH, F, Cl, Br, I, CF_3, NO_2, NH_2, CN, COOH, $COOC_1-C_4$-alkyl, C_1-C_4-alkylamino, CCl_3, C_1-C_4-dialkylamino, $SO_2-C_1-C_4$-alkyl, SO_2phenyl, $CONH_2$, $CONH-C_1-C_4$-alkyl, CONHphenyl, $CONH-C_1-C_4$-alkylphenyl, $NHSO_2-C_1-C_4$-alkyl, $NHSO_2$phenyl, $S-C_1-C_4$-alkyl,


C_1-C_4-alkyl,
C_0-C_4-alkylphenyl,

CHO, $CH_2-O-C_1-C_4$-alkyl, $-CH_2O-C_1-C_4$-alkylphenyl, $-CH_2OH$, $-SO-C_1-C_4$-alkyl, $-SO-C_1-C_4$-alkylphenyl, $-SO_2NH_2$, $-SO_2NH-C_1-C_4$-alkyl

and two radicals form a bridge $-O-(CH_2)_{1,2}-O-$,

B may be



and

A may be hydrogen, chlorine, bromine, iodine, fluorine, CF_3, nitro, OH, O-C_1-C_4-alkyl, O-C_1-C_4-alkylphenyl, NH_2, branched and unbranched C_1-C_6-alkyl, CN, NH-CO-R^{33}, where R^{33} is hydrogen, C_1-C_4-alkyl or phenyl and

R^{31} is hydrogen, C_1-C_6-alkyl, $(CH_2)_t$-K and

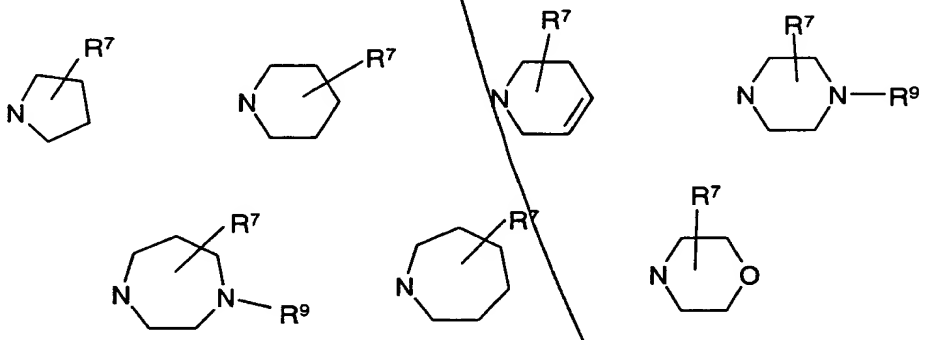
R^{32} is hydrogen, C_1-C_6-alkyl, -CO-R^8, SO_2-R^8, -(C=N)-R^8, -CO-NHR^8, -CO-OR^8 and —(C=N)-NHR^8 and

R^{33} is hydrogen and C_1-C_4-alkyl and

t is 0,1,2,3,4 and

K is phenyl which may carry at most two radicals R, is $NR^{k1}R^{k2}$ (where R^{k1} and R^{k2} are as defined for R^{41} and R^{42} respectively), NH-C_1-C_4-alkylphenyl, pyrrolidine, piperidine, 1,2,5,6-tetrahydropyridine, morpholine, trihydroazepine, piperazine, which may also be substituted by an alkyl radical C_1-C_6-alkyl, and homopiperazine, which may also be substituted by an alkyl radical C_1-C_6-alkyl, and

R^5 may be hydrogen, C_1-C_6-alkyl, NR^7R^9 and



and

R^7 is hydrogen, C_1-C_6-alkyl, C_1-C_4-alkylphenyl, phenyl, it also being possible for the rings to be substituted by up to two radicals R^{71}, and

R^{71} is OH, C_1-C_6-alkyl, O-C_1-C_4-alkyl, chlorine, bromine, iodine, fluorine, CF_3, nitro, NH_2, and

R^8 is hydrogen, C_1-C_6-alkyl, phenyl, C_1-C_4-alkylphenyl, it also being possible for the ring to be substituted by up to two radicals R^{81}, and

R^{81} is OH, C_1-C_6-alkyl, O-C_1-C_4-alkyl, chlorine, bromine, iodine, fluorine, CF_3, nitro, NH_2, and

R^9 is hydrogen, $COCH_3$, CO-O-C_1-C_4-alkyl, $COCF_3$, branched and unbranched C_1-C_6-alkyl, it being possible for one or two hydrogens of the C_1-C_6-alkyl radical to be substituted in each case by one of the following radicals: OH, O-C_1-C_4-alkyl and phenyl, and for the phenyl ring also to carry one or two of the following radicals: iodine, chlorine, bromine, fluorine, branched and unbranched C_1-C_6-alkyl, nitro, amino, C_1-C_4-alkylamino, C_1-C_4-dialkylamino, OH, O-C_1-C_4-alkyl, CN, CF_3, SO_2-C_1-C_4-alkyl,

and the tautomeric forms, possible enantiomeric and diastereomeric forms thereof, the prodrugs thereof and pharmacologically tolerated salts.

2. A compound of the formula I or II as claimed in claim 1 in which

R^1 is hydrogen, branched and unbranched C_1-C_6-alkyl, it also being possible for one C atom of the alkyl radical to carry OR^{11} or a group R^5, where

R^{11} is hydrogen or C_1-C_4-alkyl, and

R^2 is hydrogen, chlorine, fluorine, bromine, iodine, branched and unbranched C_1-C_6-alkyl, nitro, CF_3, CN, $NR^{21}R^{22}$, NH-CO-R^{23}, OR^{21}, where

R^{21} and R^{22} are, independently of one another, hydrogen or C_1-C_4-alkyl, and

R^{23} are [sic] hydrogen, C_1-C_4-alkyl or phenyl, and

R^3 is $-O-(CH_2)_o-(CHR^{31})_m-(CH_2)_n-R^5$, where

R^{31} is hydrogen, C_1-C_4-alkyl, OH and O-C_1-C_4-alkyl,

m,o is [sic], independently of one another, 0, 1 or 2, and

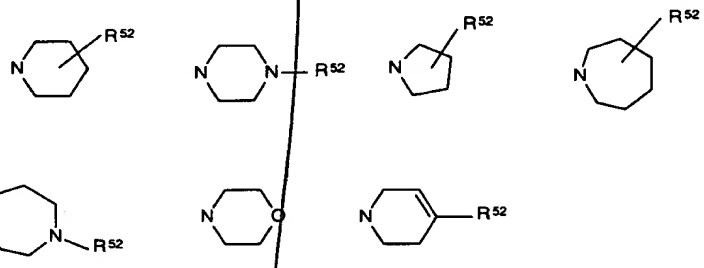
n is 1, 2, 3 or 4, and

R^4 is hydrogen, branched and unbranched C_1-C_6-alkyl, chlorine, bromine, fluorine, nitro, cyano, $NR^{41}R^{42}$, $NH-CO-R^{43}$, OR^{41}, where

R^{41} and R^{42} are, independently of one another, hydrogen or C_1-C_4-alkyl, and

R^{43} are [sic] C_1-C_4-alkyl or phenyl, and

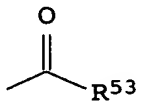
R^5 is $NR^{51}R^{52}$ or one of the following radicals



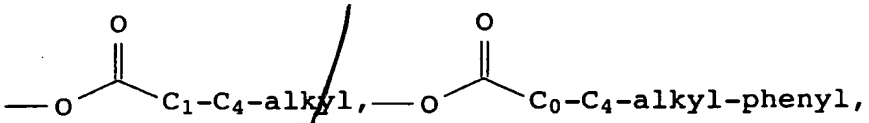
where

R^{51} is hydrogen and branched and unbranched C_1-C_6-alkyl, and

R^{52} [lacuna] hydrogen, branched and unbranched C_1-C_6-alkyl, phenyl,

 , $-SO_2R^{53}$, in which

R^{53} is branched or unbranched $O-C_1$-C_6-alkyl, phenyl, branched or unbranched C_1-C_4-alkyl-phenyl, where one hydrogen in the C_1-C_6-alkyl radical in R^{52} and R^{53} can, independently of one another, be substituted by one of the following radicals: OH, $O-C_1$-C_4-alkyl, cyclohexyl, cyclopentyl, tetrahydronaphthyl, cyclopropyl, cyclobutyl, cycloheptyl, naphthyl and phenyl, where the carbocycles of the R^{52} and R^{53} radicals may also, independently of one another, carry one or two of the following radicals: branched or unbranched C_1-C_6-alkyl, branched or unbranched $O-C_1$-C_4-alkyl, OH, F, Cl, Br, I, CF_3, NO_2, NH_2, CN, COOH, $COOC_1$-C_4-alkyl, C_1-C_4-alkylamino, CCl_3, C_1-C_4-dialkylamino, SO_2-C_1-C_4-alkyl, SO_2phenyl, $CONH_2$, $CONH-C_1$-C_4-alkyl, CONHphenyl, $CONH-C_1$-C_4-alkyl-phenyl, $NHSO_2-C_1$-C_4-alkyl, $NHSO_2$phenyl, $S-C_1$-C_4-alkyl,



C_1-C_4-alkyl,

C_0-C_4-alkyl-phenyl,

CHO, CH_2-O-C_1-C_4-alkyl, -CH_2O-C_1-C_4-alkyl-phenyl, -CH_2OH, -SO-C_1-C_4-alkyl, -SO-C_1-C_4-alkyl-phenyl, SO_2NH_2, -SO_2NH-C_1-C_4-alkyl
and two radicals form a bridge -O-$(CH_2)_{1,2}$-O-,

and the tautomeric form, possible enantiomeric and diastereomeric forms thereof, the prodrugs thereof, and possible physiologically tolerated salts.

3. A compound of the formula I or II as claimed in claim 1 in which

R^1 is hydrogen, branched and unbranched C_1-C_6-alkyl, it also being possible for one C atom of the alkyl radical to carry OR^{11} or a group R^5, where

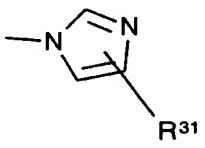
R^{11} is hydrogen or C_1-C_4-alkyl, and

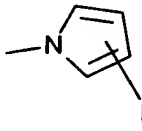
R^2 is hydrogen, chlorine, fluorine, bromine, iodine, branched and unbranched C_1-C_6-alkyl, nitro, CF_3, CN, $NR^{21}R^{22}$, NH-CO-R^{23}, OR^{21}, where

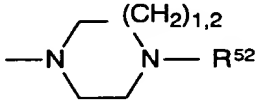
R^{21} and R^{22} independently of one another are hydrogen or C_1-C_4-alkyl and

R^{23} is hydrogen, C_1-C_4-alkyl or phenyl, and

R^3 is







and

R^{31} is hydrogen, CHO and -$(CH_2)_o$-$(CHR^{32})_m$-$(CH_2)_n$-R^5, where

R^{32} is hydrogen, C_1-C_4-alkyl, OH and O-C_1-C_4-alkyl,

m,o independently of one another are 0, 1 or 2 and

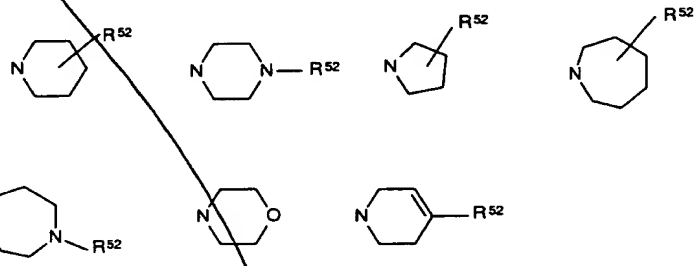
n is 1, 2, 3 or 4, and

R^4 is hydrogen, branched and unbranched C_1-C_6-alkyl, chlorine, bromine, fluorine, nitro, cyano, $NR^{41}R^{42}$, NH-CO-R^{43}, OR^{41}, where

R^{41} and R^{42} independently of one another are hydrogen or C_1-C_4-alkyl and

R^{43} is C_1-C_4-alkyl or phenyl, and

R^5 is $NR^{51}R^{52}$ or one of the radicals below



where

R^{51} is hydrogen and branched and unbranched C_1-C_6-alkyl and

R^{52} is hydrogen, $COCH_3$, CO-O-C_1-C_4-alkyl, $COCF_3$, branched and unbranched C_1-C_6-alkyl, it being possible for one hydrogen of the C_1-C_6-alkyl radical to be substituted by one of the following radicals: OH, O-C_1-C_4-alkyl and phenyl and for the phenyl ring also to carry one or two of the following radicals: chlorine, bromine, fluorine, branched and unbranched C_1-C_4-alkyl, nitro, amino, C_1-C_4-alkylamino, C_1-C_4-dialkylamino, OH, O-C_1-C_4-alkyl, CN, SO_2-C_1-C_4-alkyl,

and the tautomeric forms, possible enantiomeric and diastereomeric forms thereof, the prodrugs thereof, and possible physiologically tolerated salts.

4. A compound as claimed in any of claims 1 to 3, where R^2 is in position 3 and R^3 is in position 4 or R^2 is in position 4 and R^3 is in position 3 relative to the benzimidazole ring.

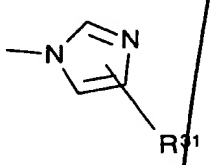
5. A compound as claimed in any of claims 1 to 4, where R^1 and R^4 are hydrogen.

6. A compound as claimed in any of claims 1 to 5, where

R^2 is hydrogen, branched or unbranched C_1-C_6-alkyl, nitro, CN, NH_2, O-C_1-C_4-alkyl.

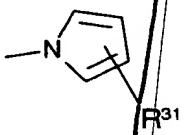
7. A compound as claimed in any of claims 1 or 3 to 6 where

(i) for R^3 being



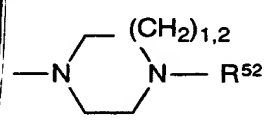
R^{31} is hydrogen or $-(CH_2)_p-R^5$, where
p is 1 or 2 and
R^{52} may be hydrogen, branched and unbranched C_1-C_6-alkyl, where one hydrogen of the C_1-C_6-alkyl radical may be substituted by one of the following radicals: OH, O-C_1-C_4-alkyl and phenyl, and where the phenyl ring may also carry one or two of the following radicals: chlorine, bromine, fluorine, branched and unbranched C_1-C_4-alkyl, nitro, amino, C_1-C_4-alkylamino, C_1-C_4-dialkylamino, OH, O-C_1-C_4-alkyl, CN, SO_2-C_1-C_4-alkyl;

(ii) for R^3 being



R^{31} is hydrogen or $-(CH_2)_p-R^5$, where
p is 1 or 2 and
R^{52} may be hydrogen, branched and unbranched C_1-C_6-alkyl, where one hydrogen of the C_1-C_6-alkyl radical may be substituted by one of the following radicals: OH, O-C_1-C_4-alkyl and phenyl, and where the phenyl ring may also carry one or two of the following radicals: chlorine, bromine, fluorine, branched and unbranched C_1-C_4-alkyl, nitro, amino, C_1-C_4-alkylamino, C_1-C_4-dialkylamino, OH, O-C_1-C_4-alkyl, CN, SO_2-C_1-C_4-alkyl;

and (iii) for R^3 being



where R^{52} is hydrogen, branched and unbranched C_1-C_6-alkyl, where one hydrogen of the C_1-C_6-alkyl radical may be substituted by one of the following radicals: OH,

O-C_1-C_4-alkyl and phenyl, and where the phenyl ring may also carry one or two of the following radicals: chlorine, bromine, fluorine, branched and unbranched C_1-C_4-alkyl, nitro, amino, C_1-C_4-alkylamino, C_1-C_4-dialkylamino, OH, O-C_1-C_4-alkyl, CN, SO_2-C_1-C_4-alkyl.

8. A compound as claimed in any of claims 1, 2 or 4 to 6, where R^3 is -O-$(CH_2)p$-R^5 with p equal to 2, 3 or 4.

A2 9. A compound as claimed in any of claims 1, 2 or 4 to 7, where R^5 is a 6-membered ring and R^{52} is an optionally substituted phenyl ring.

10. A drug comprising besides conventional vehicles and ancillary substances a compound as claimed in any of claims 1 to 9.

11. The use of compounds of the formula I as claimed in any of claims 1 to 10 for producing drugs for treating diseases in which pathologically elevated PARP activities occur.

12. The use of compounds of the formula I as claimed in claim 11 to 6 for producing drugs for treating neurodegenerative diseases and neuronal damage.

13. The use as claimed in claim 11 for treating neurodegenerative diseases and neuronal damage induced by ischemia, trauma or massive bleeding.

14. The use as claimed in claim 11 for treating stroke and craniocerebral trauma.

15. The use as claimed in claim 11 for treating Alzheimer's disease and Huntington's disease.

16. The use of compounds of the formula I as claimed in claim 11 for producing drugs for the treatment or prophylaxis of damage due to ischemia.

17. The use of compounds of the formula I as claimed in claim 11 for producing drugs for treating epilepsies, in particular generalized epileptic seizures, such as, for example, petit mal and tonoclonic seizures and partial epileptic seizures such as temporal lope [sic], and complex partial seizures.

18. The use of compounds of the formula I as claimed in claim 11 for producing drugs for treating damage to the kidneys after renal ischemia, damage caused by drug therapy such as, for

example, during cyclosporin therapy, and for treatment during and after kidney transplants.

19. The use of compounds of the formula I as claimed in claim 11 for producing drugs for treating damage to the heart after cardiac ischemia.

20. The use of compounds of the formula I as claimed in claim 11 for producing drugs for treating microinfarcts such as, for example, during and after heart valve replacement, aneurysm resections and heart transplants.

21. The use of compounds of the formula I as claimed in claim 11 for producing drugs for treatment in cases of revascularization [sic] of critically narrowed coronary arteries such as, for example, PTCA and bypass operations or critically narrowed peripheral arteries, especially leg arteries.

22. The use of compounds of the formula I as claimed in claim 11 for producing drugs for treating acute myocardial infarct and damage during and after medical or mechanical lysis thereof.

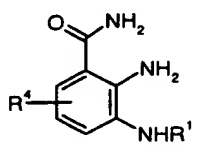
23. The use of compounds of the formula I as claimed in claim 11 for producing drugs for treating tumors and metastasis thereof.

24. The use of compounds of the formula I as claimed in claim 11 for producing drugs for treating sepsis of multi-organ failure such as, for example, during septic shock and "acute respiratory distress syndrome".

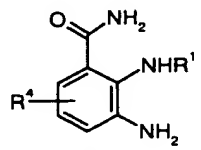
25. The use of compounds of the formula I as claimed in claim 11 for producing drugs for treating immunological diseases such as inflammations and rheumatic diseases such as, for example, rheumatoid arthritis.

26. The use of compounds of the formula I as claimed in claim 11 for producing drugs for treating diabetes mellitus.

27. A compound of the formula XX or XXI



XX



XXI

in which

R, R^1 and R^2 are as defined in the preceding claims,

and salts thereof.

28. A process for preparing compounds of the formula XX or XXI and salts thereof, which comprises reacting 2-halo-3-nitrobenzoic acid esters with a suitable diamine in a polar solvent in the presence of a base, followed by hydrogenation of the nitro group with hydrogen in the presence of a suitable catalyst.

29. The use of compounds of the formula XX or XXI in the synthesis of PARP inhibitors.

30. An in vitro detection method for PARP inhibitors, which comprises

a) incubating an unsupported or supported polyADP-ribosylatable target with a reaction mixture comprising
   a1) a PARP,
   a2) a PARP activator; and
   a3) a PARP inhibitor or an analyte in which at least one PARP inhibitor is suspected;
b) carrying out the polyADP-ribosylation reaction; and
c) determining the polyADP-ribosylation of the target qualitatively or quantitatively using an anti-poly(ADP-ribose) antibody.

31. A method as claimed in claim 23, wherein PARP is preincubated with the PARP activator and the PARP inhibitor or an analyte in which at least one PARP inhibitor is suspected before the polyADP ribosylation reaction is carried out.

32. A method as claimed in either of claims 23 or 24, wherein the polyADP-ribosylatable target is a histone protein.

33. A method as claimed in any of claims 23 to 25, wherein the PARP activator is activated DNA.

34. A method as claimed in any of claims 23 to 26, wherein the polyADP ribosylation reaction is started by adding NAD^+.

35. A method as claimed in any of claims 23 to 27, wherein the unsupported target is labeled with an acceptor fluorophore.

36. A method as claimed in claim 28, wherein the polyADP ribosylation of the unsupported target is determined using anti-poly(ADP-ribose) antibody which is labeled with a donor fluorophore which is able to transfer energy to the acceptor fluorophore.

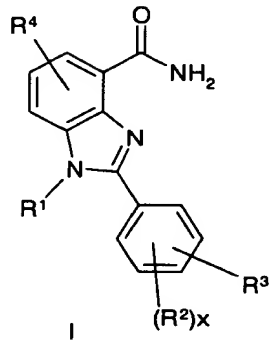
37. A method as claimed in either of claims 28 and 29, wherein the target is biotinylated histone, and the acceptor fluorophore is coupled thereto via avidin or streptavidin.

38. A method as claimed in either of claims 29 and 30, wherein the anti-poly(ADP-ribose) antibody carries a europium cryptate as donor fluorophore.

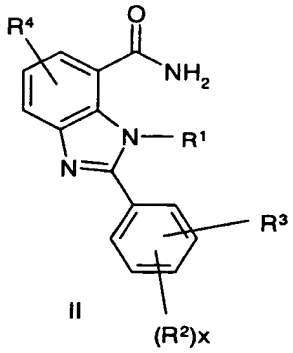
Substituted 2-phenylbenzimidazoles, the preparation and use thereof

Abstract

The present invention relates to novel 2-phenylbenzimidazoles of the general formula I or II



I



II

in which the radicals are as defined in the description, and the tautomeric forms, possible enantiomeric and diastereomeric forms thereof, the prodrugs thereof, and possible physiologically tolerated salts, the preparation and use thereof.